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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/573,386 | 11/13/2006 | Toshisada Yano | 07541.0009 | 9341 |

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| EXAMINER | |
|---|---|
| CHANG, CELIA C | |

| ART UNIT | PAPER NUMBER |
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| 1625 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/573,386 | YANO ET AL. | |
| | Examiner | Art Unit | |
| | Celia Chang | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/06, 1/21/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

**1.** This application is a 371 of PCT/JP2004/013775.

A preliminary amendment was filed on Nov. 13, 2006.

Claims 1-18 are pending.

**2.** Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

A review of the specification (US 20070082927 pregrant publication) provided the following observation:

> *[0032] The invention provides (1) A Compound of the Formula (I): wherein X is OH or lower alkylsulfonyloxy; [0033] Ar is optionally substituted aryl or optionally substituted heteroaryl; [0034] n is an integer of 1 to 4; [0035] m is an integer of 0 to 1; [0036] R.sup.1 is hydrogen; [0037] R.sup.2 is OH or [0038] R.sup.1 and R.sup.2 taken together may form a single bond; excluding that [0039] 1) n is 2; m is 0; R.sup.1 and R.sup.2 taken together may form a single bond; and Ar is optionally substituted phenyl and [0040] 2) n is 3; m is 0; R.sup.1 and R.sup.2 taken together may form a single bond; and Ar is phenyl, a pharmaceutically acceptable salt or a **solvate** thereof. (2) The compound described in (1) wherein n is 3 or 4, a pharmaceutically acceptable salt, or a **solvated** thereof. (3) The compound described in (1) wherein m is 1, a pharmaceutically acceptable salt or a **solvate** thereof. (4) The compound described in (1) wherein n is 3; m is 1; and Ar is optionally substituted phenyl, a pharmaceutically acceptable salt or a **solvate** thereof. (5) The compound described in (1) wherein n is 3; m is 1; R.sup.1 is hydrogen; R.sup.2 is OH; and [0041] Ar is optionally substituted phenyl, a pharmaceutically acceptable salt or a **solvate** thereof. (6) The compound described in (1) wherein n is 3; m is 1; R.sup.1 and R.sup.2 taken together may form a single bond; and Ar is optionally substituted phenyl, a pharmaceutically acceptable salt, or a **solvate** thereof. (7) The compound described in (1) wherein n is 3; m is 0; R.sup.1 and R.sup.2 taken together may form a single bond; and Ar is substituted phenyl, a pharmaceutically acceptable salt, or a **solvate** thereof. (8) The compound described in (1) wherein Ar is optionally substituted heteroaryl, a pharmaceutically acceptable salt or a **solvate** thereof. (9) The compound described in (1) wherein n is 3; m is 0; R.sup.1 and R.sup.2 taken together may form a single bond; and Ar is optionally substituted heteroaryl, a pharmaceutically acceptable salt or a **solvate** thereof. (10) A pharmaceutical composition containing the compound described in any one of (1) to (9). (11) The pharmaceutical composition described in (10) having NMDA receptor antagonistic activity. (12) The pharmaceutical composition described in (11) having NR1/NR2B*

*receptor antagonistic activity. (13) A pharmaceutical composition which contains the compound described in any one of (1) to (9) and which is an analgesic or a medicament for treating migraine, stroke, head injury, Alzheimer's disease, Parkinson's disease, or tinnitus. (14) A pharmaceutical composition which contains the compound described in any one of (1) to (9) and which is an analgesic. (15) A method for alleviating pain or treating migraine, stroke, head injury, Alzheimer's disease, Parkinson's disease, or tinnitus comprising administrating the compound described in any one of (1) to (9). (16) A method for alleviating pain comprising administrating the compound described in any one of (1) to (9). (17) Use of the compound described in any one of (1) to (9) for manufacturing an analgesic or a medicament for treating migraine, stroke, head injury, Alzheimer's disease, Parkinson's disease, or tinnitus. (18) Use of the compound described in any one of (1) to (9) for manufacturing an analgesic. (19) A compound of the formula (1): wherein X is OH or lower alkylsulfonyloxy; [0042] Ar is optionally substituted aryl or optionally substituted heteroaryl; [0043] n is an integer of 1 to 4; [0044] m is an integer of 0 to 1; [0045] R.sup.1 is hydrogen; [0046] R.sup.2 is OH or [0047] R.sup.1 and R.sup.2 taken together may form a single bond; excluded that [0048] 1) n is 1 or 2; m is 0; R.sup.1 and R.sup.2 taken together may form a single bond; and Ar is optionally substituted phenyl and [0049] 2) n is 3; m is 0; R.sup.1 and R.sup.2 taken together may form a single bond; and Ar is phenyl, a pharmaceutically acceptable salt or a* ***solvate*** *thereof.*

*[0088] The compound (I) may be a* ***solvate*** *of water or acetonitrile. The number of hydration of the hydrated compound of the present invention may be fluctuated generally in accordance with a synthetic method, a refining method, or crystallization conditions and it may be in a range of 1 to 5 water molecules per 1 molecule of the compound.*

The limited description as recited above provided no actual reduction to practice of any compound to form solvate/hydrate with any solvent or water. A solvate/hydrate is normally a multiple component product with specific weight relationship (see dictionary definition) for which no description was found. No description as to how a solvate/hydrate can be formed i.e. process of making or what was the characteristics of such compound i.e. molecular formula, physical property, crystalline packing etc. The state of the art is that in possession of only a compound does not warrant any predictability of solvate/hydrate formation (See Braga et al. p.40).

Therefore, the specification is insufficient in providing "written description" for the claimed scope "solvate thereof" when in possession of compound per se.

**3.** Claims 10-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

A review of the specification (US 20070082927 pregrant publication) provided the following observation:

> *Abstract*
> *A piperidine derivative of the formula (I) is found to bind specifically with the NR1/NR2B receptor and usable as an analgesic (pain treatment drug).*
>
> *[0005] …….. Recently, cloning of genes of the NMDA receptor has been done from brains of rats and mice to make it clear that the NMDA receptor is composed of two subunits of NR1 and NR2 (reference to Non-patent Documents Nos. 3 and 4). The NR2 subunit contains four subfamilies (NR2A, 2B, 2C, and 2D) (reference to Non-patent Document Nos. 5 and 6). It is said that the NR1/NR2A receptors are mainly relevant to development of memory and learning acquirement and that the NR1/NR2B receptor is mainly relevant to nerve degeneration cell death and transmittance of pains (reference to Non-patent Document Nos. 7 and 8).*
>
> *[0007] However, since the competitive NMDA receptor antagonists may possibly antagonize not only the NR1/NR2B receptor but also NR1/NR2A receptor, in the case of long time administration of the drugs for Alzheimer's disease or the like, there is a risk of deterioration of learning capability and memory formation.*
>
> *[0031] Based on the results of investigations, inventors of the present invention have found that certain kinds of piperidine derivatives cause strong antagonistic actions for the NR1/NR2B receptor and a remarkable analgesic effect and causes no side effect such as psychotic disturbance and accordingly have completed the following inventions.*

The above description clearly identified that NR2A and NR2B are different subset of NMDA receptor and long time administration of nonspecific NR2B antagonists will cause deterioration of learning and memory. While the specification provided using of compounds and dosage for treating pain based on NR2B antagonistic activity of the claimed compounds, no description or reducing to practice of the compounds being able to have efficacy on the NR2A receptor which is relevant to learning and memory i.e treating Alzheimer's disease. Further, there is no nexus of such compounds having efficacy in treating stroke, head injury, parkinson's disease or tinnitus for which complex mechanism in patho-physiology are involved.

Further, in absence of nexus, there is insufficient provision in the specification how to manufacture a "medicament" for treating stroke, head injury, parkinson's disease or tinnitus with effective dosage. There is no actual reduction to practice of such a composition or process for treating the above condition. The pharmceutical compound art is highly unpredictable especially the field of NMDA receptor art has developed to identified subunits which are different in properties, physiological functionality and binding requirement. The specification with limited description of formula I being NR2B receptor antagonists is in sufficient in providing "written description" for the broad scope of making composition and treating stroke, head injury, parkinson's disease or tinnitus.

**4.** Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the scope of the claims.

The claims encompassed the scope of "solvates of the compounds" for which no description or enabling support can be found in the specification. Please note that each solvate is a different "chemical identity" and there should never be any doubt in this century as to the chemical identity of a material (see Suddon). Unlike formation of salts between a pharmaceutically acceptable acid and an organic base compound of the claims, the formation of "solvates" must find descriptive and enabling support for such claimed scope because absent of specific description, one having ordinary skill in possession of compounds would not be able to offer any predictability of which one will form what solvate (see Braga p.3640). A survey of the specification indicated there is no description of which solvent can form solvate with the compounds, under what condition will such solvates be obtained, and whether the solvates will have consistent properties to be considered inclusive as being a "Markush" alternative of the compounds.

No examples, no process of making, no starting material or operability can be found for any compound encompassed by the Markush formula to have the ability in forming what solvate. Therefore, absent of description and enabling disclosure, the specification is insufficient in supporting the "claimed" *scope* of "solvates of the compounds".

**5.** Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the *scope* of the claims.

It was clearly identified in the specification that NR2A and NR2B are different subset of NMDA receptor and long time administration of nonspecific NR2B antagonists will cause deterioration of learning and memory. In absent of factual support, no nexus was provided that the process of making "analgesic" composition and treating pain would have any efficacy in treating non-pain related disorders such as stroke, head injury, Alzheimer's disease, Parkinson's disease or tinnitus. Especially, the pain relieve dosage was known to have deteriorative effect on symptoms of these other disorders.

**6.** Claims 1-18 being drawn to compounds of formula I and pharmaceutically acceptable acid addition salts being useful in manufacturing analgesic compositions or used as analgesic i.e. treating pain are allowable. Structurally closest compound is found in Amsterdam et al. WO 02/30422 see p.12 second from bottom. The difference is that the prior art compound does not have R2 being hydroxyl. Modification of the prior art compound to the instant claims is lacking since the compound is sigma receptor binding. Other analogous art such as US 7,435,744; Collins et al. CA 100:79478; Casanova et al. FR 2105119 or Pinard et al. disclosed structural close analgesic compound wherein the linker between the phenyl ring and the piperidinyl ring does not contain a "oxo" substitution. Oxo substituted linker were contemplated but with less desirable activity (see Pinard p.2175 table 1, compound 17). Therefore, no suggestion to modify attributes of the prior art compounds with particularity of the instant claims.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*OACS/Chang*
*Aug. 5, 2009*

*/Celia Chang/*
*Primary Examiner*
*Art Unit 1625*